

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number  
WO 2005/014718 A1

(51) International Patent Classification<sup>7</sup>: C08L 67/04, A61L 17/12, 27/18, 27/58, 27/54, 31/06, 31/14

(21) International Application Number:  
PCT/GB2004/003101

(22) International Filing Date: 19 July 2004 (19.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0317192.3 19 July 2003 (19.07.2003) GB

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:  
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2005/014718 A1

(54) Title: HIGH STRENGTH BIOREABSORBABLE CO-POLYMERS

(57) Abstract: A polymer composition comprising poly-glycolic acid (PGA) and at least one other monomer to give a composition having a tensile strength of at least 1100MPa.

## HIGH STRENGTH BIORESORBABLE CO-POLYMERS

The present invention relates to polymer compositions and artefacts made therefrom. In particular the present invention relates to polymers having high mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body. More particularly the invention relates to bioresorbable glycolic acid-containing co-polymers and to implantable medical devices made therefrom.

10 Polymer compositions comprising poly-glycolic acid (PGA) and glycolic acid-containing co-polymers have an established use for medical implants. It has also been proposed that certain mechanical properties may be improved by extruding PGA melts or by drawing PGA in a plastic state. Isotropic PGA has a tensile strength of

15 between 50 to 100 MPa and a tensile modulus of between 2 and 4 GPa. A commercial product (SR-PGA) comprising PGA fibres in a PGA matrix has a flex strength and modulus of 200 – 250 MPa and 12 – 15 GPa, respectively. It is also reported in the literature that melt spun PGAs have tensile strength of about 750 MPa and a

20 modulus from 15 to 20 GPa. In US Patent No. 4968317 an example of a drawn PGA is stated to have a tensile strength of about 600MPa.

Although PGAs having improved strength characteristics are known, none of the known materials have the mechanical properties

25 approaching those of the metals conventionally used for load bearing implantable medical devices. A commercial alloy used for orthopaedic implant devices, known as Ti-6-4, comprises titanium with 6% aluminium and 4% vanadium and has a tensile strength in the range of 800 to 1000MPa and a modulus in the order of 100GPa.

One possible reason that PGA and glycolic acid-containing co-polymers cannot currently be processed to achieve the desired strength of metals is that when the polymers are processed by common methods to produce orientated fibres (e.g. stretching the

5 material at a constant rate in a heated chamber or tank) additional polymer crystallisation occurs during the process. The crystals in the polymer act such that they prevent further polymer orientation. This crystallisation of the polymer limits the mechanical properties that can be achieved by drawing glycolic acid-containing co-polymers to

10 around 800MPa, as described in the prior art.

We have found that polymer compositions comprising glycolic acid-based co-polymers may be processed such that the resultant composition has significantly greater strength, typically of the order of greater than 1100MPa or 1150MPa or 1200MPa with a

15 commensurate increase in modulus, typically in excess of 20GPa, 21 GPa or 22 GPa.

In accordance with the present invention there is provided a polymer composition comprising glycolic acid as a co-polymer with at least one other bioresorbable monomer, or a functional derivative of said

20 co-polymer, having a tensile strength of at least 1200MPa.

In accordance with the present invention there is provided a polymer composition comprising glycolic acid as a co-polymer with at least one other bioresorbable monomer, or a functional derivative of said co-polymer, having a tensile strength of at least 1100MPa.

25 The polymer composition gains this level of tensile strength by means of a novel processing method that results in an orientated structure, for example an orientated fibre.

The present invention further provides an artefact comprising a polymer composition including glycolic acid or a functional derivative

30 thereof having a tensile strength of at least 1200MPa.

The present invention also provides an artefact comprising a polymer composition including glycolic acid or a functional derivative thereof having a tensile strength of at least 1100MPa.

The polymer composition may be comprised entirely of glycolic acid-

5 based co-polymer or a derivative thereof, or may comprise a glycolic acid-based co-polymer-containing blend with other polymers. Preferably the polymer composition is entirely glycolic acid-based co-polymer.

Similarly, artefacts formed from the polymer compositions of the 10 invention may consist wholly of the polymer compositions of the invention or may be composites consisting only partially of the polymer compositions of the invention.

Aptly the artefact contains 10 to 80% by volume of the polymer compositions of the invention, suitably the artefact contains up to 15 60% by volume of the polymer compositions of the invention, preferably the artefact contains at least 40% by volume of the polymer compositions of the invention and typically the artefact contains approximately 50% by volume of the polymer compositions of the invention.

20 We have found that in order to achieve the high strength exhibited by the compositions of the invention it is necessary that the glycolic acid-containing co-polymer be rendered into an amorphous state and then immediately drawn to form a highly orientated structure.

This can be achieved by first processing isotropic glycolic acid- 25 based co-polymer granules to form fibres or filaments, thereafter passing the fibres into a quenching bath to form an amorphous structure. Polymer compositions of the present invention may then be produced by drawing the quenched, amorphous glycolic acid based co-polymer. Preferably this is a drawing process which

minimises the time polymer is exposed to elevated temperatures, thus minimising the time for the polymer to crystallise.

In accordance with another aspect of the invention there is provided

5 a process for the manufacture of glycolic acid-based co-polymer compositions comprising increasing polymer chain orientation of a substantially amorphous polymer by drawing at localized points within the mass.

Suitably this comprises the steps of forming glycolic acid-based co-polymer or a functional derivative thereof into fibres, for example by melt extrusion or solution spinning; quenching the fibres then subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.

Aptly fibres of amorphous glycolic acid-based co-polymer-containing polymers may be prepared by solution spinning or melt extruding the polymer through a die; the filament is then rapidly chilled to produce a substantially amorphous material. Typical chilling methods include blowing a cold gas onto the filament as it is produced or by passing the filament through a bath of a suitable cold liquid, e.g. water, 20 silicone oil.

A suitable drawing method is zone heating. In this process a localised heater is moved along a length of fibre which is held under constant tension. This process is used in the zone-drawing process as described by Fakirov in Oriented Polymer Materials, S Fakirov, 25 published by Hüthig & Wepf Verlag, Hüthig GmbH. In order to carry out this zone heating fibre can be passed through a brass cylinder. A small part of the cylinder inner wall is closer to the fibre, this small region locally heats the fibre, compared to the rest of the brass cylinder, localising the drawing of the fibre to this location, see figure 30 1. A band heater can be placed around the brass cylinder to allow it

to be heated above room temperature. This heated brass cylinder can then be attached to the moving cross-head of a tensile testing machine and the fibre to be drawn suspended from a beam attached to the top of the testing machine. To draw the fibre a weight

5 can be attached to the lower end of the fibre, the brass cylinder heated to the desired temperature and the cross-head moved to the lower end of the fibre, see figure 2. The polymer draws where the fibre is closest to the brass cylinder, as the cross-head is moved up the length of the fibre, then a length of the fibre can be drawn.

10 Suitably the fibre can be held taut using a small stress, which is typically below the yield point of the material at ambient temperatures. The fibre can then be heated locally to a temperature which is above the softening point ( $T_g$ ) but below the melting point such that localised drawing of the polymer occurs, the whole fibre

15 can be treated by movement of either or both the fibre and heated zone such that the full length of the fibre is drawn. This first drawing of the polymer may produce a polymer with improved molecular alignment and therefore strength and modulus. In this first step the conditions are selected such that the material does not substantially

20 crystallise during the process, this requires that either the temperature of the polymer is below the temperature at which crystallisation occurs,  $T_c$ , or if the polymer is above  $T_c$  the speed at which the heated zone moves along the fibres is fast enough such that the polymer cools below  $T_c$  before it has time to crystallise.

25 Further improvements can be made by subsequent treatments, where the stress applied to the fibre or the zone temperature is increased or both. Both the strength of the fibre and the softening point increase as the degree of molecular alignment improves. The process can be repeated many times, until the desired properties are

30 reached. A final annealing step can be carried out in which the material crystallises under tension in the process; this can further improve the mechanical properties and improve the thermal stability of the final fibre.

In an embodiment of this aspect of the invention there is provided an artefact comprising a poly-glycolic acid in accordance with the invention. For example, the glycolic acid-containing co-polymer fibres can be mixed with other components to form the artefacts.

- 5 These other components may be polymers, bioresorbable polymers, non-polymeric materials or combinations thereof.

Aptly the bioresorbable polymer comprises a poly-hydroxy acid, a poly-caprolactone; a polyacetal; a poly-anhydride or mixture thereof; the polymer comprises poly-propylene, poly-ethylene, poly-methyl 10 methacrylate, epoxy resin or mixtures thereof whilst the non-polymeric component comprises a ceramic, hydroxyapatite, tricalcium phosphate, a bioactive factor or combinations thereof.

Suitably the bioactive factor comprises a natural or engineered protein, a ribonucleic acid, a deoxyribonucleic acid, a growth factor, 15 a cytokine, an angiogenic factor or an antibody.

Artefacts according to the present invention can aptly be manufactured by placing appropriate lengths of strengthened glycolic acid-containing co-polymer fibre into moulds, adding the other components then compression moulding. Alternatively, the 20 strengthened fibres can be pre-mixed with the other components then compression moulded.

In an alternative processing method, artefacts according to the present invention can be manufactured by forming a polymeric component in the presence of the strengthened fibres by in situ 25 curing of monomers or other precursors for said polymeric component.

Preferably the monomers used in this process do not liberate any by-products on polymerisation as these can compromise the properties of the artefact.

Aptly at least one of the monomers used in said in situ curing process is a ring-opening monomer that opens to form a poly-hydroxy acid. Typically at least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or a mixture thereof.

5 The polymer itself may be produced from reacting/incorporating/combining or by other means the glycolide or glycolic acid with at least one other monomer.

Incorporation of the at least one other monomer into the polymer composition can be achieved by any known means and for example 10 maybe by ring polymerisation or transesterification.

Suitable monomers may include ring opening monomers like for instance lactide (& its isomers), trimethylene, carbonate, p-dioxanone,  $\epsilon$ -caprolactone, 2-methyl glycolide, 2,3,2-dimethyl glycolide, 1,5-dioxapane, 1,4-dioxapane, 3,3-dimethyltrimethylene 15 carbonate, glycosalicate, depsipeptides (morpholine 2,5-dione and related structures).

Aptly other suitable monomers may include Hydroxyacids, for instance including, lactic acid, caproic acid, hydroxyl benzoic acid and aminoacid esters.

20 In other embodiments the monomers may suitably be diacids (e.g. adipic acid, diglycolic acid), diols (e.g. propylene glycol, butane diol, or unsaturated diols like for instance hydroxyl propyl fumarates), addition monomers (e.g. spiro monomers, isocyanates, divinyl ethers), Anhydrides (e.g. sebacic anhydride).

25 The at least one other bioresorbable monomer component of the polymer composition according to the present invention may include a number of different monomers, in equal or different amounts.

Aptly the ratio of glycolic acid to bioresorbable monomer or monomers may be 95%PGA to 5% other monomer(s).

Typically the ratio of glycolic acid to other bioresorbable monomer/monomers will be 70:30%, 75:25%, 80:20%, 90:10%, 95:5% or 98:2%

5 Aptly there will be greater than 70% glycolic acid, in the polymer composition according to the present invention but aptly could also be greater than 75, 80, 90 or 95% glycolic acid to other bioresorbable monomer/monomers.

Thus the bioresorbable monomer/monomers percentage may be  
10 aptly between 30 to 1%, 25 to 1%, 20 to 1%, 15 to 1%, 10 to 1% or 5 to 1%.

The polymer compositions of the invention are useful for the production of medical devices, particularly implantable devices where it is desirable or necessary that the implant is resorbed by the  
15 body. Thus, artefacts in accordance with the present invention include sutures; tissue-engineering scaffolds or scaffolds for implantation; orthopaedic implants; reinforcing agents for long fibre composites used in resorbable load bearing orthopaedic implants; complex shaped devices, for example formed by injection moulding  
20 or extruding composites formed by mixing short lengths of chopped fibres with poly-lactic acid; or bone fixation devices, for example formed from relatively large diameter rods (e.g., greater than 1mm) of the compositions of the invention.

The invention will now be illustrated by the following example.

25

#### Example 1

PGA:PLA co-polymer (98% PGA, 2% PLA) was extruded into a water bath to produce a translucent fibre of approx 0.5mm diameter. This fibre was then suspended vertically and a weight of 200g was

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applied. A heated cylinder of brass with a hole of approx 15mm apart from a small section with a 2mm diameter hole, through which the PGA fibre passes, was heated to a temperature of 90°C and moved along the fibre at a speed of 200 mm/min. The fibre 5 produced was found to have a strength of greater than 1200 MPa and a modulus of greater than 20 GPa.

#### Example 2

A PGA – PLLA (poly-glycolic acid – poly L-lactide) (95:5%) co-polymer was extruded into a water bath to produce a translucent 10 fibre of approximately 0.48mm diameter. This fibre was then suspended vertically and a weight of 100g was applied. A heated cylinder of brass with a hole of approximately 15mm apart from a small section with a 2mm diameter hole, through which the PGA fibre passes, was heated to a temperature of 90°C and moved along 15 the fibre at a speed of 500mm/min.

The resultant fibre was tested in tension using an Instron 5566 machine fitted with a 100N load cell. Two pieces of the fibre were drawn and tested, the results are:

20	Strength/MPa	Modulus/GPa
Fibre 1	1154	21.4
Fibre 2	1115	20.8

**Claims**

1. A polymer composition comprising glycolic acid (GA) as a co-polymer with at least one other bioresorbable monomer, or a 5 functional derivative of said co-polymer, having a tensile strength of at least 1100MPa.
2. A polymer composition as claimed in claim 1, in which there are two bioresorbable monomers.
3. A polymer composition as claimed in either claim 1 or claim 2 10 in which at least one other bioresorbable monomer is polylactic acid (PLA).
4. A polymer composition as claimed in any preceding claim in which at least one other bioresorbable monomer is poly L-lactic acid (PLLA).
- 15 5. A polymer composition as claimed in any preceding claim in which the GA composition is at least 70% glycolic acid.
6. A polymer composition as claimed in claim 5 in which the GA composition is at least 75, 80, 85, 90 or 95% glycolic acid.
7. A polymer composition as claimed in claim 4 or 5 in which the 20 polymer composition is around 95% glycolic acid.
8. A polymer composition as claimed in any one of claims 4 or 5 in which the polymer composition is around 98% glycolic acid.
9. An artefact comprising strengthened glycolic acid polymer composition as according to any one of claims 1 to 7.
- 25 10. A polymer composition as claimed in any preceding claim in which the fibres have a tensile modulus of at least 20GPA.

11. A polymer composition as claimed in any preceding claim in which the fibres have a tensile modulus of at least 21GPa.
12. A polymer composition as claimed in any preceding claim in 5 which the fibres have a tensile modulus of at least 22GPa.
13. A process for the manufacture of a polymer composition as claimed in any one of the preceding claims which includes the steps of:
  - 10 a) forming the polymer composition comprising glycolic acid as a copolymer with at least one other bioresorbable monomer, or a functional derivative thereof, into fibre;
  - b) quenching the fibres then;
  - 15 c) subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.
14. A process according to claim 13 in which the fibre forming method is melt extrusion or solution spinning.
15. A process according to claims 13 or 14 in which the 20 quenched, tensioned fibres are subjected to zone-heating.
16. A process according to claims 13 to 15 in which the quenched, tensioned fibres are subjected to at least two separate drawing steps, each drawing step performed under identical or different conditions.
- 25 17. An artefact comprising a polymer composition, or a functional derivative thereof according to any one of claims 1 to 12 or

11. A polymer composition as claimed in any preceding claim in which the fibres have a tensile modulus of at least 21GPa.
12. A polymer composition as claimed in any preceding claim in 5 which the fibres have a tensile modulus of at least 22GPa.
13. A process for the manufacture of a polymer composition as claimed in any one of the preceding claims which includes the steps of:
  - 10 a) forming the polymer composition comprising glycolic acid as a copolymer with at least one other bioresorbable monomer, or a functional derivative thereof, into fibre;
  - b) quenching the fibres then;
  - 15 c) subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.
14. A process according to claim 13 in which the fibre forming method is melt extrusion or solution spinning.
15. A process according to claims 13 or 14 in which the 20 quenched, tensioned fibres are subjected to zone-heating.
16. A process according to claims 13 to 15 in which the quenched, tensioned fibres are subjected to at least two separate drawing steps, each drawing step performed under identical or different conditions.
- 25 17. An artefact comprising a polymer composition, or a functional derivative thereof according to any one of claims 1 to 12 or

when produced by a process according to any one of claims 13 to 16.

18. An artefact of claim 17 comprising at least two polymer components.
19. An artefact of claim 18 comprising 10% to 80% by volume the polymer composition or a functional derivative thereof according to any one of claims 1 to 12 or when produced by a process according to any one of claims 13 to 16.
- 10 20. An artefact of any one of claims 17 to 19 in which at least one of the polymer components is bioresorbable.
21. An artefact of claim 20 in which the bioresorbable polymer comprises a poly-hydroxy acid, a poly-lactic acid, a poly-caprolactone, a poly-acetal or a poly-anhydride.
- 15 22. An artefact of any one of claims 17 to 21 comprising at least one non-bioresorbable polymer component.
23. An artefact of claim 22 in which the non-bioresorbable polymer comprises poly-propylene, poly-ethylene, poly-methyl methacrylate or epoxy resin.
- 20 24. An artefact of any one of claims 17 to 23 further containing at least one non-polymeric component.
25. An artefact of claim 25 in which the non-polymeric component comprises a ceramic, hydroxyapatite or tricalcium phosphate.
26. An artefact of claim 25 or 26 in which the non-polymeric component comprises a bioactive factor.
27. An artefact of claim 27 in which the bioactive component comprises a natural or engineered protein, a ribonucleic acid,

a deoxyribonucleic acid, a growth factor, a cytokine, an angiogenic factor or an antibody.

28. An artefact according to any one of claims 17 to 27 in which  
5 the artefact is in the form of a medical device.

29. An artefact of claim 28 in which the device is a suture, a scaffold for tissue engineering or implantation, an orthopaedics implant, a complex shaped device or a bone fixation device.

10 30. A process to manufacture an artefact according to any one of claims 17 to 29 comprising the steps of:

- a) placing appropriate lengths of strengthened glycolic acid polymer composition as according to any one of claims 1 to 7, into moulds;
- 15 b) adding any other components (and mixing);
- c) compression moulding to the desired shape.

31. A process to manufacture an artefact according to any one of claims 17 to 29 comprising the steps of

- 20 a) forming a polymeric component in the presence of strengthened glycolic acid polymer composition as according to any one of claims 1 to 7 and;
- b) in situ curing of the monomers or other precursors to form said polymeric component and artefact.

32. A process for the manufacture of artefacts according to any  
25 one of the claims 17 to 29 which includes the step of: compression moulding other polymeric, non-polymeric or

blend of polymeric and non-polymeric components in the presence of said fibres.

33. A process of claim 30 or 31 in which includes the step of  
5 compression moulding other polymeric, non-polymeric or blend of polymeric and non-polymeric components in the presence of said fibres.

34. A process of claim 32 or 33 in which further includes the step of: forming a polymeric component in the presence of said  
10 fibres by in situ curing of monomers or other precursors for said polymeric component.

35. A process of claim 34 in which the monomer used does not liberate a by-product on polymerisation.

36. A process of claim 34 or 35 in which at least one of the  
15 monomers is a ring opening monomer that opens to form a poly hydroxyl acid.

37. A process of claim 36 in which at least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or mixtures thereof.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2004/003101

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7	C08L67/04	A61L17/12	A61L27/18	A61L27/58	A61L27/54
	A61L31/06	A61L31/14			

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08L A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

3 November 2004

Date of mailing of the International search report

17/11/2004

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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